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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **Controlled-release medical preparations.**

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(73) Proprietor: **AB LEO**
Box 941
S-251 09 Helsingborg (SE)

(72) Inventor: **Lindahl, Ake Rikard**
Ringduvevägen 50
S-274 00 Skurup (SE)
Inventor: **Ekman, Bo Magnus**
Manstigen 9
S-216 19 Malmö (SE)

(74) Representative: **Thylén, Eva**
c/o AB Leo Patent Department Box 941
S-251 09 Helsingborg (SE)

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Description

The present invention relates to an oral pharmaceutical controlled-release preparation which has a biphasic release profile of pharmacologically active agent(s).

Prior art

Oral preparations having a biphasic release profile of the active drug(s) are previously known.

Common medical preparations disclosing a biphasic release profile of one or more pharmacologically active agents include a tablet core from which the active substance is released and a surrounding coating from which the same or a different substance is released. The surrounding coating is applied in a conventional coating step. The release from the core may occur at a slow, moderate or rapid rate.

An oral preparation of this type is disclosed in e.g. the US patent 3,538,214. This patent discloses a pharmaceutical preparation consisting of a tablet core comprising a medicament, which is soluble in gastrointestinal fluids, and a coating on said core. The coating consists of a polymer substance which remains substantially intact and insoluble in the gastro-intestinal fluids. Fine particles of a readily water-soluble substance are randomly distributed in the coating. Furthermore, it is disclosed in the patent that the preparation can be provided with an additional coating which e.g. may contain another pharmacologically active substance.

Another preparation characterized by biphasic release profile is disclosed in the EP patent publication 13131. From the specification and disclosed examples it is obvious that this kind of preparation includes an active ingredient incorporated in a controlled release matrix comprising a higher aliphatic alcohol and a hydrated water soluble hydroxy alkyl cellulose. On this matrix, which slowly releases the active ingredient is applied a standard film coating solution, in which a second active agent is dissolved or suspended.

As will be obvious from the following description and examples the present invention is concerned with a different type of preparation, wherein the slow release of the active ingredient included in the core is obtained by the dissolution rate limiting properties of special type of film surrounding the core and not as according to the EP application by the rate-limiting properties of the core matrix.

Objects of the invention

It is an object of the present invention to provide a novel pharmaceutical tablet having a biphasic release of the drug(s).

A second object of the present invention to provide a method according to which such tablets can be prepared using one single coating process.

A third object is to provide a simple and useful method of obtaining a wide variety of biphasic release patterns.

A forth object is to provide a medical preparation which can offer variable release patterns for different drugs or drug combinations.

Summary of the invention

The present invention concerns a controlled-release coated pharmaceutical preparation comprising a drug tablet and a coating applied thereon, wherein the coating essentially consists of a film-forming polymer which is insoluble in water and gastrointestinal fluids and a water-soluble pore-creating material being randomly distributed in said polymer. The preparation is characterized in that the pore-creating material partially or totally consists of a drug active substance in sufficient amounts to produce a pharmacological or therapeutical effect.

The present invention also provides a method of preparing this controlled-release preparation comprising the steps of dissolving the said polymer in a solvent, preparing a suspension or solution of the pore-creating material, providing a pharmaceutical tablet combining the suspension or solution of pore-creating material and solution of the polymer to form a coating fluid, applying the coating fluid in the form of a solution or suspension to the tablet and drying the coating fluid on the tablet to provide a polymer-coated tablet having water-soluble pore-creating material randomly distributed within the polymer.

The preparation according to the invention is advantageous for two principally different controlled-release embodiments.

One preferred embodiment of the invention concerns medical preparation of at least two different pharmacologically or drug active substances which should be provided in combination. According to this embodiment the drug in the core may be e.g. potassium chloride and the drug active substance included in the pore-creating material may be an instant release diuretic such as metolazone, clopamide, ethacrynic acid, hydroflumethiazide, methylclothiazide, quinethazone, trichloromethiazide, chlorothiazide, chlorothalidone, cyclothiazide, furosemide, hydrochlorothiazide, polythiazide, bendroflumethiazide, cyclopenthiazide, mefruside, and bumetanide.

Another example is a core containing theophylline or a theophylline salt such as ethylene diamine theophyllinate or choline theophyllinate, and the pore creating material being a beta-2-stimulant such as salbutamol or terbutaline.

In this connection it should be pointed out that the US patent 3,538,214 discussed previously discloses of the combination potassium chloride and hydrochlorothiazide, but in this preparation the

hydrochlorothiazide is present in an additional overcoating (cf Example 11). Consequently, the method to combine two different active substances in one and the same tablet is much more complicated according to the method known from the US patent than according to the present invention, and the disclosure of the US patent actually teaches away from the present invention.

According to another embodiment the pore-creating material includes the same drug active agent as the core. Such a formulation provides a rapid release giving rise to initially effective plasma levels which are then maintained by the controlled release action of the preparation. Example of a drug suitable for such a preparation is phenylpropanol amine (PPA) which is used i.a. as a nasal and sinus decongestant. It is also widely used as an appetite suppressant. CNS stimulation caused by PPA, if used in the late part of the day, may interfere with sleep at night. An ideal formulation of PPA would produce effective plasma concentrations during day-time, i.e. for 16 hours, while it gives low or negligible plasma concentrations during night.

Other interesting fields where the same active substance is present in the core and as (part of) the pore-creating material in the coating are penicillins, cephalosporines, benzdiazepines, calcium antagonists, e.g. diltiazem and short-acting hypnotics.

The release pattern of the active substance from the tablet core may be adapted to fit various requirements by varying the ratio of pore-creating material versus coating polymer, the combination of pore-creating substances and the coating thickness. It is often preferred to choose the parameters, which give the coating such properties that a constant, i.e. zero order, release of the active drug in the core is obtained.

Detailed description of the invention

The filmforming polymeric substances used for the coating mixtures according to the present invention are pharmaceutically acceptable filmforming polymers which are substantially water-insoluble but soluble in organic solvents, e.g. ketones. Examples of such substances are cellulose derivatives, acrylic polymers, and other high molecule polymers such as ethylcellulose, cellulose acetate, cellulose propionate, cellulose butyrate, cellulose valerate, cellulose acetate propionate, polyvinyl acetate, polyvivyl formal, polyvinyl butyral, ladder polymer of sesquiphenyl siloxane, polymethyl methacrylate, polycarbonate, polyester, coumarone-indene polymer, polybutadiene, vinyl chloride-vinyl acetate copolymer, ethylene-vinyl acetate copolymer and vinyl chloride-propylene-vinyl acetate terpolymer.

The polymeric membranes applied may also comprise a plasticizer. As examples of plasticizers may be mentioned triacetin, acetylated monoglyceride, rape oil, olive oil, sesame oil, acetyltributyl citrate, acetyltriethyl citrate glycerin, sorbitol, diethyl oxalate, diethyl malate, diethylfumarate, diethyl succinate, diethyl malonate, dioctylphthalate, dibutyl sebacetate, triethyl citrate, tributyl-citrate, glycerol tributyrate, polyetheylene glycol, propylene glycol, and mixtures of the above. Especially preferred are plasticizers such as acetyl tributyl citrate, polyethylene glycol, blown castor oil and glyceryl triacetate.

The amount of plasticizer may vary between 0.1 and 4% weight by weight of the coating fluid.

The pore-creating material according to the present invention can be any substance which gives the desired pharmacological effect, is pharmaceutically acceptable and fulfils the following requirements:

A) When coated in suspension form:

1. It must be soluble in water (gastro-intestinal fluids).
2. It must be essentially insoluble in the organic solvents used in the coating process, e.g. in acetone, methyl ethyl ketone.
3. It should have a particle size of 0.5—100 µm.

B) When coated in solution form:

1. It must be soluble in water (gastro-intestinal fluids).
2. It must be essentially soluble in the organic solvents used in the coating process, e.g. in acetone, methyl ethyl ketone.
3. It should have a particle size of 0.5—100 µm

provided that in A) and B) above the pore-creating material does not include (pharmacologically inactive amounts of) calcium carbonate, calcium phosphates, magnesium citrate, magnesium oxide, sodium bicarbonate, potassium bicarbonate, tetraethanolamine, propionic acid, sorbic acid, salicylic acid and cellulose acetate ftalate, potassium chloride or sodium chloride.

According to the present invention a wide variety of coatings can be used. Depending on the manufacturing process and the fact that, when in the living body, the coating is affected by several factors (influence of different pH, different enzymes motility of the intestines) it is obvious that some filmforming polymers are more suitable than others. Thus it has been found that a copolymer of vinyl acetate and vinyl chloride gives good results. Another especially preferred polymer is a terpolymer containing 80—95% weight per weight of vinylchloride, 1—19% weight per weight vinyl acetate and 1—10% weight per weight of vinyl alcohol.

The amount of pore-creating material which consists of the drug active substance depends on the level of the substance initially required. In order to get the desired slow release pattern of the drug in the core it may sometimes be required that pore-creating material includes additional amounts of water-soluble

material, which meet with the requirements mentioned above and which is pharmaceutically acceptable and pharmacologically essentially inactive at the amounts used. The weight ratio total amount pore-creating material to polymer depends on the polymer chosen and the release pattern desired. The additional inactive material, which if required is included in the pore-creating material, may e.g. consist of sucrose, polyvinylpyrrolidone or a polyethylene glycol. If a vinyl acetate copolymer or a vinyl acetate-vinyl chloride-vinyl alcohol terpolymer is used it is suitable that the ratio total pore-creating material to polymer varies between 0.1 and 20, preferably 1 and 5 and especially 1.5 and 3.

The coating fluid is produced in the following manner:

A polymer which preferably could be a terpolymer containing (w/w%) 80—95% VC (vinylchloride), 1—19% VAC (vinylacetate), and 1—10% VOH (vinylalcohol) is dissolved in a solvent, e.g. acetone, methylenechloride, methylethylketone, or mixtures of acetone and ethanol, acetone and methylenechloride.

The pore-creating particles including drug active substance and optionally additional inactive substance are are ground either by dry milling in a ball mill or by wet-milling in a glass bead milling device to a defined particle size, preferably between 0.5 µm and 100 µm. The particles are dispersed in solvents or mixtures of solvents, such as those previously mentioned, and mixed with the polymer solution to form the coating fluid.

Depending on the size and area of the tablet the coating weight may vary between 10 and 170 mg per tablet and the coating thickness may vary between 25 and 300 µm, preferably between 50 and 200 µm.

The invention is further illustrated by but not limited to the following examples, wherein the Examples 1—3 disclose preparations in which the same active drug is present in the core and in the coating.

Example 1

Phenylpropanolamine 75 mg Tablet:

Phenylpropanolamine	50 mg
Polyethylenoxide 6000	60 mg
Sucrose M sieved	72.6 mg
Polyvinylpyrrolidone	5 mg
Magnesiumstearate	2 mg
Ethanol	

The ingredients were mixed except for the Mg-stearate; moistened with ethanol and dried. After drying the powder was mixed with Mg-stearate and the mixture was compressed to tablets.

Coating suspensions	A	B	C
Filmforming terpolymer	7 mg	10 mg	14 mg
Acetyltributyl citrate	2.23 mg	2.23 mg	2.23 mg
Blown castor oil	1.67 mg	1.67 mg	1.67 mg
Phenylpropanolamine	25 mg	25 mg	25 mg
Polyvinylpyrrolidone	1.34 mg	1.34 mg	1.34 mg
Acetone	526 mg	526 mg	526 mg

Sieved phenylpropanolamine was dispersed in acetone solutions of the polymer and plasticizer. The suspensions were coated on to the tablets in a coating pan. The filmforming polymer used in this example consisted of a terpolymer of (VC)M, (VAC)N, (VOH)O, wherein VC is polyvinylchloride, VAC is vinylacetate and VOH is vinylalcohol. M=31, N=1 and O=2.

The phenylpropanolamine diffusion from the three types of tablets having different amounts of polymer in the coating was followed by using the paddle method described in the United States Pharmacopeia, 19th rev., Mack Publishing Co., Easton Pa., 1975, p. 651 (=USP XX).

As can be seen from the accompanying figure all three types of tablets give a rapid release of the drug

during the first hour. After that a slow release dissolution over a long period of time can be obtained. The rate of the slow release can be varied by changing the amount of polymer.

Example 2
Tablet

Cefaclorum®	340 mg
Avicel® PH	20 mg
Powdered sucrose H	143 mg
Aerosil®	13 mg
Stearin talc 50%	33 mg

The ingredients were mixed in a double-cone mixer and compressed to tablets.

Coating

Cefaclorum® (sieved)	60 mg
Filmforming polymer	14.3 mg
Acetyltributyl citrate	2.7 mg
Blown castor oil	2.2 mg
Polyvinyl pyrrolidone	1.9 mg
Acetone	

The filmforming polymer consisted of a (VC)M, (VAC)N, (VOH)O terpolymer, wherein M=100, N=1 and O=8.

Example 3
Nitrazepam 6 mg

Tablet

Nitrazepam	4 mg
Powdered sucrose	120 mg
Polyethylene oxide 6000	110 mg
Polyvinylpyrrolidone	5 mg
Magnesium stearate	2 mg

The ingredients except for the Mg-stearate were mixed and moistened with ethanol. After drying Mg-stearate was added and the powder was compressed to tablets.

Coating:

Filmforming polymer according to Example 1	9.8 mg
Acetyltributyl citrate	1.87 mg
Blown castor oil	1.40 mg
Nitrazepam (sieved)	2 mg
Micronized sucrose	23 mg
Acetone	530 mg

Example 4

The following example discloses a preparation, in which different drug active substances are present in the core and in the coating.

The tablet core contained 1 g potassium chloride.

The coating suspension had the following composition:

Filmforming polymer according to Example 1	180 g
Micronized powdered sucrose (particle size 1—10 µm)	409 g
Acetyl tributyl citrate	40.9 g
Blown castor oil	31.2 g
Bendroflumethiazide	34.0 g
Acetone ad	4400 g

The coating process is performed in a coating pan and the coating fluid is sprayed onto the tablets with an airless spray-coating device. Five thousand tablets are coated and the average membrane weight is 60 mg per tablet.

Example 5

The procedure according to Example 1 was followed but nitrocellulose was used as filmforming substance instead of the terpolymer.

Example 6

The procedure according to Example 1 was followed but cellulose acetate was used as filmforming substance instead of the terpolymer.

Claims

1. A controlled-release pharmaceutical preparation having biphasic release profile, comprising a drug tablet and a coating applied thereon, wherein the coating essentially consists of a filmforming polymer which is insoluble in water and gastro-intestinal fluids and a water-soluble pore-creating material being randomly distributed in said polymer characterized in that the pore-creating material includes a drug active substance in a therapeutically effective amount.

2. Preparation according to Claim 1 characterized in that the pore-creating material includes a drug active substance different from that in the drug core.

3. Preparation according to Claim 1 characterized in that the drug active substance in the pore-creating material is the same substance as the one present in the drug core.

4. Preparation according to any one of the preceding Claims characterized in that the pore-creating material also include a substance, which is soluble in water and gastro-intestinal fluids and therapeutically essentially inactive in the amount used, said amount being sufficient to give a preselected release profile.

5. Preparation according to Claim 2 characterized in that the drug in the core is potassium chloride and that the drug active substance included in the pore-creating material is an instant release diuretic.

6. Preparation according to Claim 3 characterized in that the drug active substance is selected from phenylpropanol amine, a penicillin, cephalosporin, a benzodiazepine, a calcium antagonist and a short-acting hypnotic.

7. Preparation according to any of the Claims 1—5 characterized in that the filmforming polymer is selected from cellulose derivatives, acrylic polymers and vinyl polymers.

8. Preparation according to any of the preceding Claims characterized in that the filmforming polymer is a terpolymer consistin of vinylchloride, vinylacetate and vinylalcohol.

9. A method of preparing the controlled-release preparation according to Claim 1 comprising the steps of dissolving the polymer in a solvent, preparing a suspension or solution of the core-creating material including the drug active substance and solution of the polymer to form a coating fluid, applying the coating fluid in the form of a solution or suspension to the drug tablet and drying the coating fluid on the tablet to provide a polymer-coated tablet having water-soluble pore-creating material randomly distributed within the coating.

10. Method according to Claim 9 characterized in that the pore-creating material includes a drug active substance different from that in the drug core.

11. Method according to Claim 9 characterized in that the drug active substance in the pore-creating material is the same substance as the one present in the drug core.

12. Method according to any of the Claims 9—11 characterized in that the pore-creating material also includes a substance that is soluble in water and gastrointestinal fluids and therapeutically essentially inactive in the amount used, said amount being sufficient to give a preselected release profile.

13. Method according to Claim 10 characterized in that the drug in the core is potassium chloride and that the drug active substance included in the pore-creating material is an instant release diuretic.

14. Method according to Claim 11 characterized in that the drug active substance is selected from phenylpropanol amine, a penicillin, cephalosporin, a benzodiazepine, a calcium antagonist and a short-circuiting hypnotic.

15. Method according to any of the Claims 10—14 characterized in that the filmforming polymer is selected from cellulose derivatives, acrylic polymers and vinyl polymers.

16. Method according to any of the Claims 10—15 characterized in that the filmforming polymer is a terpolymer consisting of vinylchloride, vinylacetate and vinylalcohol.

Patentansprüche

1. Pharmazeutisches Präparat mit geregelter Wirkstoffabgabe mit einem Zweiphasen-Freisetzungsprofil, bestehend aus einer Arzneimitteltablette und einem darauf angebrachten Überzug, wobei der Überzug im wesentlichen aus einem filmbildenden Polymer, welches in Wasser und gastrointestinalen Flüssigkeiten unlöslich ist, und einem wasserlöslichen porenbildenden, im genannten Polymer willkürlich verteilten Material besteht, dadurch gekennzeichnet, daß das porenbildende Material einen Arzneimittelwirkstoff in einer therapeutisch wirksamen Menge enthält.

2. Präparat nach Anspruch 1, dadurch gekennzeichnet, daß das porenbildende Material einen Arzneimittelwirkstoff, der verschieden ist von jenem im Arzneimittelkern, enthält.

3. Präparat nach Anspruch 1, dadurch gekennzeichnet, daß der Arzneimittelwirkstoff im porenbildenden Material dieselbe Substanz wie die im Arzneimittelkern vorhandene ist.

4. Präparat nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das porenbildende Material auch eine Substanz beinhaltet, die in Wasser und gastrointestinalen Flüssigkeiten löslich und in der verwendeten Menge therapeutisch im wesentlichen inaktiv ist, wobei die genannte Menge ausreicht ein vorbestimmtes Freisetzungsprofil zu ergeben.

5. Präparat nach Anspruch 2, dadurch gekenneichnet, daß das Arzneimittel im Kern Kaliumchlorid und daß der im porenbildenden Material enthaltene Arzneimittelwirkstoff ein Diureticum mit sofortiger Freisetzung ist.

6. Präparat nach Anspruch 3, dadurch gekennzeichnet, dass der Arzneimittelwirkstoff aus Phenylpropanolamin, Penicillinen, Cephalosporinen, Benzodiazepinen, Calciumantogonisten und Hypnoticum mit kurzer Wirkungsdauer ausgewählt ist.

7. Präparat nach einem der Ansprüche 1—5, dadurch gekennzeichnet, daß das filmbildende Polymer aus Cellulosederivaten, Acrylpolymeren und Vinylpolymeren ausgewählt ist.

8. Präparat nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das filmbildende Polymer ein Terpolymer, bestehend aus Vinylchlorid, Vinylacetat und Vinylalkohol, ist.

9. Verfahren zur Herstellung des Präparates mit geregelter Wirkstoffabgabe nach Anspruch 1, gekennzeichnet durch die Stufen der Lösung des Polymers in einem Lösungsmittel, der Bereitung einer Suspension oder Lösung des porenbildenden Materials, das den Arzneimittelwirkstoff beinhaltet, und der Lösung des Polymers zwecks Bildung einer Überzugsflüssigkeit, des Auftragens der Überzugsflüssigkeit in Form einer Lösung oder Suspension auf die Arzneimitteltablette und der Trocknung der Überzugsflüssigkeit auf der Tablette, um eine mit einem Polymer überzogene Tablette, welche ein wasserlösliches porenbildendes, willkürlich im Überzug verteiltes Material aufweist, zu schaffen.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß das porenbildende Material einen Arzneimittelwirkstoff, der verschieden ist von jenem im Arzneimittelkern, enthält.

11. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß der Arzneimittelwirkstoff im porenbildenden Material dieselbe Substanz wie die im Arzneimittelkern vorhandene ist.

12. Verfahren nach einem der Ansprüche 9—11, dadurch gekennzeichnet, daß das porenbildende Material auch eine Substanz enthält, die in Wasser und gastrointestinalen Flüssigkeiten löslich und in der verwendeten Menge therapeutisch im wesentlichen inaktiv ist, wobei genannte Menge ausreicht ein vorbestimmtes Freisetzungsprofil zu ergeben.

13. Verfahren nach Anspruch 10, dadurch gekennzeichnet, daß das Arzneimittel im Kern Kaliumchlorid und der im porenbildenden Material enthaltene Arzneimittelwirkstoff ein Diureticum mit sofortiger Freisetzung ist.

14. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß der Arzneimittelwirkstoff aus Phenylpropanolamin, einem Penicillin, Cephalosporin, einem Benzodiazepin, einem Calciumantagonisten und einem kurzwirksamen Hypnoticum ausgewählt ist.

15. Verfahrem nach der Ansprüche 10—14, dadurch gekennzeichnet, daß das filmbildende Polymer aus Cellulosederivaten, Acrylpolymeren und Vinylpolymeren ausgewählt ist.

16. Verfahren nach einem der Ansprüche 10—15, dadurch gekennzeichnet, daß das filmbildende Polymer ein Terpolymer, bestehend aus Vinylchlorid, Vinylacetat und Vinylalkohol, ist.

Revendications

1. Une préparation pharmaceutique à libération contrôlée ayant un profil de libération diphasique, comprenant un comprimé de médicament et un enrobage qui lui est appliqué, dans laquelle l'enrobage est essentiellement constitué d'un polymère filmogène qui est insoluble dans l'eau et dans les sucs gastro-intestinaux et d'une matière porogène soluble dans l'eau qui est répartie au hasard dans ledit polymère, caractérisée en ce que la matière porogène comprend une substance médicamenteuse active en une quantité thérapeutiquement efficace.

2. Préparation selon la revendication 1, caractérisée en ce que la matière porogène comprend une substance médicamenteuse active différente de celle du noyau médicamenteux.

3. Préparation selon la revendication 1, caractérisée en ce que la substance médicamenteuse active dans la matière porogène est la même substance que celle présente dans le noyau médicamenteux.

4. Préparation selon l'une quelconque des revendications précédentes, caractérisée en ce que la matière porogène comprend également une substance qui est soluble dans l'eau et dans les sucs gastro-intestinaux et est essentiellement thérapeutiquement inactive en la quantité utilisée, ladite quantité étant suffisante pour assurer un profil de libération préalablement choisi.

5. Préparation selon la revendication 2, caractérisée en ce que le médicament dans le noyau est le chlorure de potassium et la substance médicamenteuse active incorporée à la matière porogène est un diurétique à libération instantanée.

6. Préparation selon la revendication 3, caractérisée en ce que la substance médicamenteuse active est choisi parmi la phénylpropanolamine, une pénicilline, une céphalosporine, une benzodiazépine, un antagoniste du calcium et un hypnotique à action courte.

7. Préparation selon l'une quelconque des revendications 1 à 5, caractérisée en ce que le polymère

filmogène est choisi parmi des dérivés de la cellulose, les polymères acryliques et les polymères vinyliques.

8. Préparation selon l'une quelconque des revendications précédentes, caractérisée en ce que le polymère filmogène est un terpolymère constitué de chlorure de vinyle, d'acétate de vinyle et d'alcool vinylique.

9. Un procédé pour préparer la préparation à libération contrôlée selon la revendication 1, comprenant les étapes de dissolution du polymère dans un solvant, préparation d'une solution ou suspension de la matière porogène comprenant la substance médicamenteuse active et d'une solution du polymère pour former un fluide d'enrobage, application du fluide d'enrobage sous forme d'une solution ou suspension au comprimé médicamenteux, et séchage du fluide d'enrobage sur le comprimé pour former un comprimé à enrobage de polymère ayant une matière porogène soluble dans l'eau distribuée au hasard dans l'enrobage.

10. Procédé selon la revendication 9, caractérisé en ce que la matière porogène comprend une substance médicamenteuse active différente de celle du noyau médicamenteux.

11. Procédé selon la revendication 9, caractérisé en ce que la substance médicamenteuse active dans la matière porogène est la même substance que celle présente dans le noyau médicamenteux.

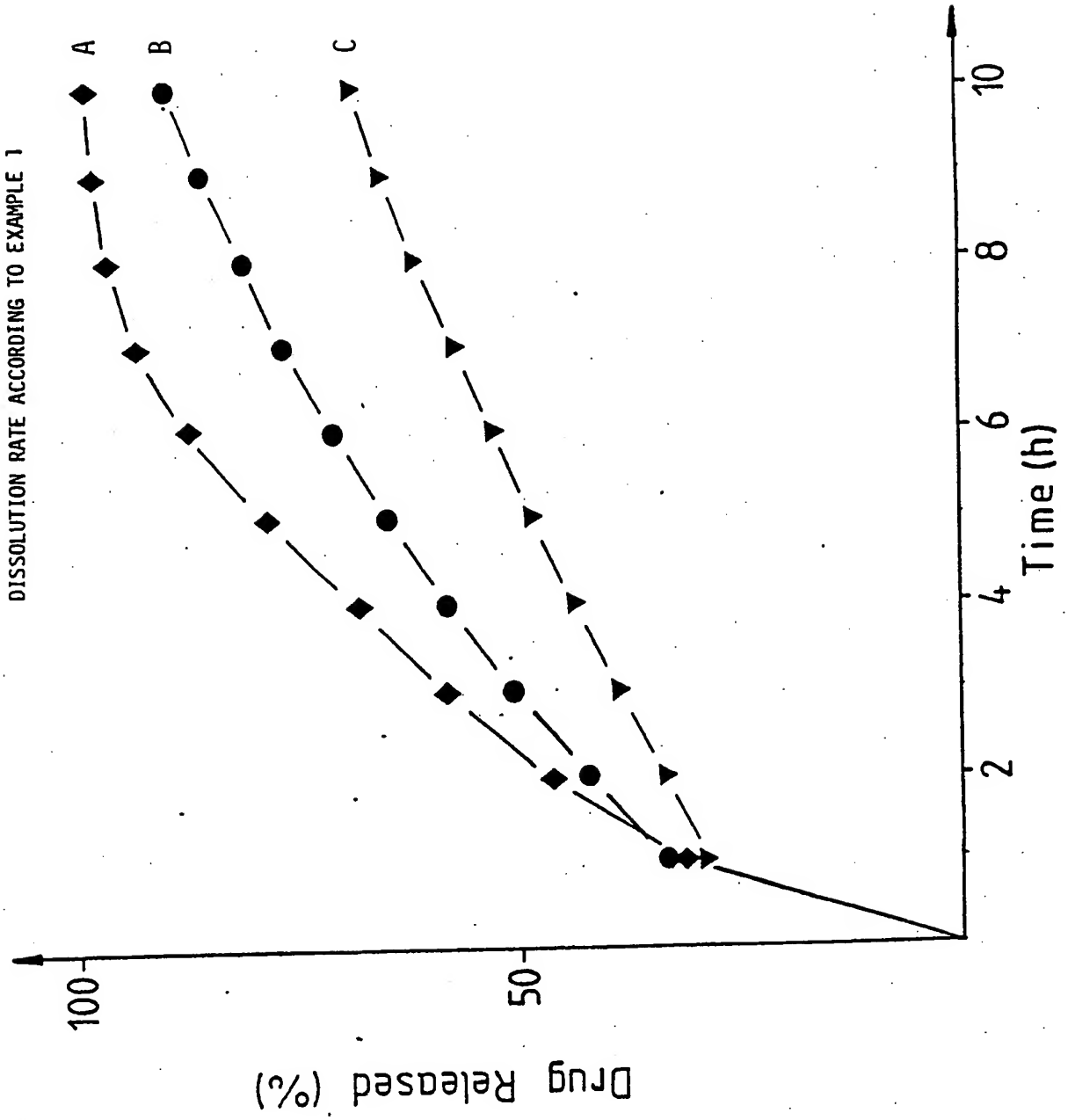
12. Procédé selon l'une quelconque des revendications 9 à 11, caractérisé en ce que la matière porogène comprend également une substance qui est soluble dans l'eau et dans les liquides gastro-intestinaux et est essentiellement thérapeutiquement inactive en la quantité utilisée, ladite quantité étant suffisante pour assurer un profil de libération préalablement choisi.

13. Procédé selon la revendication 10, caractérisé en ce que le médicament dans le noyau est le chlorure de potassium et la substance médicamenteuse active incorporée à la matière porogène est un diurétique à libération instantanée.

14. Procédé selon la revendication 11, caractérisé en ce que la substance médicamenteuse active est choisie parmi la phénylpropanolamine, une pénicilline, une céphalosporine, une benzodiazépine, un antagoniste du calcium et un hypnotique à action courte.

15. Procédé selon l'une quelconque des revendications 10 à 14, caractérisé en ce que le polymère filmogène est choisi parmi des dérivés de la cellulose, les polymères acryliques et les polymères vinyliques.

16. Procédé selon l'une quelconque des revendications 10 à 15, caractérisé en ce que le polymère filmogène est un terpolymère constitué de chlorure de vinyle, d'acétate de vinyle et d'alcool vinylique.


DISSOLUTION RATE ACCORDING TO EXAMPLE 1
A
B
C
Drug Released (%)
100
50
Time (h)
2
4
6
8
10